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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,628	01/26/2004	Veronique Trochon	1002-04	9953

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IP GROUP OF DLA PIPER LLP (US)
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
09/29/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pto.phil@dlapiper.com

Office Action Summary	Application No.	Applicant(s)	
	10/764,628	TROCHON ET AL.	
	Examiner	Art Unit	
	MARIA MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,17,21 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17,27 and 28* is/are allowed.

6)☒ Claim(s) *13,21,25,26,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/26/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/11 has been entered. Claims 13, 17, 21 and 25-30 are pending in this application.

Applicants' amendment has been sufficient to overcome the previous objections to the claims. However, the following informalities were noted.

The Declaration under 37 CFR 1.132 filed 5/13/11 in combination with applicants arguments is sufficient to overcome the rejection of claim 13, 17, 21 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Bettan et al (Bioelectrochemistry, 2000, pages 83-90; see entire document) in view of Fanslow et al (US 7,074,408; see entire document) and as evidenced by or further in view of Merkulov et al (US 6,294,368; see entire document).

Claim Objections

Claims 13, 17, 21 and 26 are objected to because of the following informalities: **These are new objections.** The recitation in claim 13, 17 and 21 of decreasing the formation of new intratumoral vessels would be more accurate if recited as --inhibiting the formation of new intratumoral vessels--. The formation is not decreased rather the occurrence of new vessels is decreased and this is due to inhibiting of the formation of the vessels.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 21, 25, 26, 29 and 30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of direct injection intratumorally or intramuscularly to a mammal comprising a melanoma or a pulmonary metastasis thereof of an expression plasmid comprising a polynucleotide coding for a therapeutic peptide consisting of an amino acid with the sequence of SEQ ID NO:2 wherein the polynucleotide is operably linked to an expression control sequence, followed by application of electric field pulses to site of the injection wherein expression of SEQ ID NO:2 results in the decrease in the number of new intratumoral vessels or a decrease in the number of intratumoral vessels, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons set forth 7/9/08 and 4/15/09 and 9/15/10restated below. The rejection has been slightly reworded based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a methods of decreasing the number, or formation of intratumoral vessels in a mammal, in a mammal with melanoma and in a mammal with pulmonary metastases by direct inoculation and electrotransfer of a nucleic acid consisting of the polynucleotide sequence of SEQ ID NO:1 operably linked to an expression control sequence. The specification teaches that the disintegrin domain of metargidin when delivered to a tumor or metastases site can cause a diminution of vessels and thus lead to a decrease in pulmonary metastases and melanoma growth. The method of claim 13 is broadly drawn to any tumor type, however, the specification and the art of record is limited to a demonstration that melanoma and pulmonary metastasis alone have been targeted by the treatment.

The disintegrin domain constitutes Met 420 to Gly 511 of the full-length metargidin. However, SEQ ID NO:1 does not encode all of the metargidin. Rather, SEQ ID NO:1 encodes **the** disintegrin domain of metargidin and this disintegrin domain is encoded by all of SEQ ID NO:1. The specification states that metargidin comprises AMEP (anti-angiogenic metargidin peptide) and is a human protein with multipotent function including blocking angiogenic functions of integrin alpha v beta, inhibition of migration and formation of capillary structures

and functions proapototically independent of modification of their cell cycle. Metargidin is a member of the adamalysin family (ADAMS) which functions in proteolysis, adhesion, fusion and intracellular signaling (see Ruben et al, US 2002/0182702 ¶ 1042). Multiple ADAMS have been identified including ADAM1, ADAMTS-1, fertilin (ADAM2), cryitestin (ADAM3), epididymal apical protein I, meltrin, MS2, TNF-a converting enzyme, Kusbanian and metargidin (see Ruben et al, ¶ 0004). Within the ADAMS, the disintegrin domain functions to prevent integrin-mediated cell to cell and cell to matrix interactions such as plated aggregration, adhesion, migration of tumor cells or neutrophils or angiogenesis. There have been multiple propositions that members of the adamalysin family have a potential to treat a myriad of conditions such as those recited here (see Ruben et al US 2002/0165377 and Young et al (US 2003/0194797 in which the role of ADAM-22 and any other ADAM protein in inhibiting angiogenesis or invasion or formation of metastases, treating cancer, treating inflammatory diseases, treating atherosclerosis, treating macular degeneration or treating psoriasis is proposed), but these propositions have not lead to the identification of any treatments that are viable options against diseases. Applicants synthesize AMEP in bacteria and demonstrate that this protein can function to inhibit adhesion of fibrinogen to vitronectin and fibronectin, inhibit endothelial cell migration, proliferation, capillary formation and stimulates proapoptosis in endothelial cells *in vitro*. *In vivo,* AMEP nucleic acid was electrotransferred to muscle of nude and C57B1/6 mice and inhibited growth of MDA-MB-231 tumor growth and formation of melanoma based pulmonary metastases in syngeneic mice.

The method of claim 13 is broadly drawn to any tumor type, however, the specification and the art of record is limited to a demonstration that melanoma and pulmonary metastasis alone have been targeted by the treatment. Specifically, the specification is limited to treatment of melanoma and of pulmonary metastasis.

Applicants provide the following results

1) Trochin-Joseph electrotransfer of the AMEP into mouse skeletal mice *in vivo* leads to rapid, stable and tightly regulated expression of the transgene suggested that a producer cell can be distant from the target.

2) The specification teaches, AMEP nucleic acid was intramuscularly injected and electrotransferred leading to expression in the muscle of nude and C57B1/6 mice, which inhibited growth of MDA-MB-231 tumor growth and inhibited formation of pulmonary metastases in syngeneic mice

3) The Declaration filed 5/8/07 teach that AMEP nucleic acid was intratumorally injected and then electrotransferred and expressed in the muscle of nude and C57B1/6 mice inhibited growth of B16F10 and C0 melanoma tumor growth and this was correlated in the Declaration filed 7/6/10 to inhibited formation of pulmonary metastases.

Regarding methods of transfer, the art teaches that the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. In fact, the specification teaches, "Likewise, most transgenic protein expression is mostly, though not exclusively, restricted to the injection site. Such experiments have failed to demonstrate widespread expression of transgenic proteins in the

brain beyond two months". As well, Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery.., the problem has been an inability to deliver genes efficiently and to obtain sustained expression". The unpredictability associated with viral based therapies has been recently highlighted in the art, see for example, Check, Nature, 2003. Leakiness of and dissemination to tissues surrounding the targeted area and hence expression of receptor in non-targeted cells is particularly lethal, "dissemination of the vector particle itself can have harmful consequences; lack of adenovirus vector specificity was directly linked to the induction of the massive systemic immune response that caused the death of Jesse Gelsinger in 1999 (see Thomas page 354, col 1). Even use of tissue specific or inducible promoters cannot offset these ill effects. Vector tropism, the duration of transgene expression and vector immunogenicity are other factors that influence the suitability of a vector for specific therapeutic applications (see Thomas, page 348, col 2). "Lentiviral transduction of muscle and liver has also been shown in animals, but, interestingly, studies in the liver have indicated that not all non-dividing cells are equally susceptible to transduction by lentivirus vectors; some cell types (such as the hepatocyte) might require cell cycling for efficient gene transfer in vivo (see Thomas, page 348, col 2)." To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. In more advanced studies related to cancer, the art teaches "to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (Russell page 1165, col 2,¶ 4-5). Local transfer is required as concentration of DNA is low and thus is sensitive to dilution (see Mir page 171, ¶ 2) and thus injection and electric pulses must be limited to the target site.

However, applicants have provided a Declaration demonstrating that the method of intramuscular and intratumoral injection of an expression plasmid followed by electropulsing results in adequate uptake of the AMEP sequences such that melanoma vascularization was reduced and the lesion was stabilized. The specification provides guidance on use of the method for treatment of melanoma and for melanoma based pulmonary metastasis.

The invention recites use of a direct inoculation and electrotransfer of nucleic acid encoding the disintegrin domain to any muscle or tumor to decrease the number of formation of intratumoral vessels in a mammal. Given the unpredictability of the art with regard to any tumor treatable by AMEP, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

Response to Amendments

Applicants' response filed on 5/13/11 has been considered but is not persuasive for the following reasons. Applicants' arguments have been based in part on a Declaration co-filed with the response. The Declarations of Dr. Mir and Dr. Attali under 37 CFR 1.132 filed 5/13/11 is sufficient to overcome in part the rejection of claims based upon 112 first paragraph as set forth in the Office action because: the results are not commensurate in scope with claim 13. Applicants have exemplified the use of AMEP delivered to a subject with melanoma and/or pulmonary metastasis wherein as a consequence of delivery the vascularization is reduced. However, claim 13 is drawn to a broad genus of subjects and tumor types. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be

developed into the claimed invention. In the decision of Genentec, Inc, v. Novo Nordisk, 42 USPQ 2d 100,(CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". This invention is so broad as to encompass a number of inoperative embodiments. For example, there is no indication that circulating levels of AMEP can reach all types of tumors such as for example those not on the circulatory route such as melanoma and pulmonary metastasis. Applicants have demonstrated possession of two species of tumor types that express receptors responsive to AMEP. However, there is no indication of success with all tumor types. It appears that AMEP must target receptors that are particularly present on melanoma cells (see Bioalliance pharma notice). Applicants have not demonstrated nor has the art provided evidence of efficacy with any cell type other than melanoma cells.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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